

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **USE OF TRICYCLIC ANTIDEPRESSANTS FOR LOCAL ANALGESIA**, the specification of which:

\_\_\_\_\_ is attached hereto.

  X   was filed on November 17, 2000 (Attorney Docket ✓  
No.: DALHO1290-1) as U.S. Application Serial No. 09/700,625 ✓  
and was amended on \_\_\_\_\_ if applicable (the "Application"). ✓

I hereby authorize and request insertion of the application serial number of the Application when officially known.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, Code of Federal Regulations ("C.F.R."), § 1.56.

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

_____ (Application Serial No.)	_____ (Filing Date)
_____ (Application Serial No.)	_____ (Filing Date)
_____ (Application Serial No.)	_____ (Filing Date)

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of the application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of the Application:

<u>PCTCA99/00449 ✓</u> (Application Serial No.)	<u>May 19, 1999 ✓</u> (Filing Date)	<u>Pending</u> (Status) (patented, pending, abandoned)
_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)
_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00 Full name of first inventor: Jana Sawynok

Inventor's signature: Jana Sawynok

Date: JAN 8/2001

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2-00 Full name of second inventor: Mike Esser

Inventor's signature: Michael Esser

Date: Jan. 10 / 2001

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3-00 Full name of third inventor: Allison Reid

Inventor's signature: Allison Reid

Date: Jan 8, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Sawynok, et al. Art Unit:  
Application No.: 09/700,625 Examiner:  
Filed: November 17, 2000  
Title: USE OF TRICYCLIC ANTIDEPRESSANTS FOR LOCAL ANALGESIA  
BOX PCT  
Commissioner for Patents  
Washington, D.C. 20231

**POWER OF ATTORNEY BY ASSIGNEE**

As a below-named assignee of the above-identified application ("Application"):

I hereby appoint the following attorneys of the assignee to prosecute the  
Application and to transact all business in the United States Patent and Trademark Office  
connected therewith:

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Registration No. 40,825  
Registration No. 27,744

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In re Application of:

Sawynok, et al.

Application No.: 09/700,625

Filed: November 17, 2000

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PATENT

Attorney Docket No.: DALHO1290-1

I hereby authorize and request insertion of the application number of the  
Application when officially known.

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By: 

Name: W. CARL BRECKENRIDGE

Title: VICE PRESIDENT RESEARCH

Date: Jan 18, 2001

PATENT  
Attorney Docket No.: DALHO1290-1  
(028614-1102)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Sawynok et al.

Application No.: 09/700,625

Filing Date: February 1, 2001

For: USE OF TRICYCLIC  
ANTIDEPRESSANTS FOR LOCAL  
ANALGESIA

Group Art Unit: 1615

Examiner: T. Ware

**CERTIFICATE OF FACSIMILE TRANSMISSION**

I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Washington, D.C., on the date below.

Stephen E. Reiter

Printed Name

Signature

Date

Commissioner for Patents  
Washington, D.C. 20231

**SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.131**

Sir:

We, Jana Sawynok, Mike Esser and Allison Reid, being duly warned, hereby individually and collectively declare and say that:

1. We are the joint co-inventors of the invention disclosed and claimed in the above-referenced application.
2. We understand that October 28, 1997 is the effective prior art date of a reference cited by the Examiner, U.S. Patent No. 5,922, 341 to Smith and Place.
3. The present invention was completed prior to October 28, 1997 during experiments performed at Dalhousie University, Halifax, Nova Scotia, Canada.

4. We understand that the Examiner has asserted that our previously submitted declaration (mailed with the response of February 11, 2002) allegedly does not provide support for second or third generation antidepressants.

5. The conception of the present invention is indeed demonstrated by the evidence provided in our previously submitted declaration because the choice of amitriptyline as a prototype antidepressant was made based on one of its recognized functions as a modulator of adenosine, and not based on its pharmaceutical classification as a particular type of antidepressant.

6. Specifically, prior work conducted in the laboratory of Dr. Jana Sawynok had demonstrated that peripheral modulation of the pain signal could be achieved by altering levels of adenosine using an adenosine kinase inhibitor. This pain modulating effect based on altering levels of adenosine was further augmented with an adenosine deaminase inhibitor. This study demonstrated that endogenous adenosine, which accumulates following peripheral inhibition of adenosine kinase, mediates pain via activation of an adenosine receptor. See Sawynok *et al.*, *Pain* 74:75-81 (1998); submitted for publication May 13, 1997; Exhibit A.

7. At this point, we conceived that a variety of compounds that exhibit an ability to modulate adenosine levels, in effect, comparable to the previously studied adenosine kinase inhibitor and/or adenosine deaminase inhibitor, could also be used in effective compositions for locally modulating pain.

8. For example, it has long been known in the art that adenosine pathways in the central nervous systems were implicated in the mode of action of several centrally active drugs including antidepressants. See, *e.g.*, Williams, *Prog. Neuropsychopharmacol. Biol. Psychiatry* 7:443-450 (1983); Abstract provided in Exhibit B. Indeed, a variety of classes of antidepressants, including both tricyclic and non-tricyclic antidepressants, have long been known to have effects on adenosine uptake. See, *e.g.*, Phillis and Wu, *Comp. Biochem. Physiol.* 72C:179-187 (1982); Exhibit C. Moreover, a specific example of a second generation or third generation antidepressant contemplated in our specification, trazodone, has also been shown to



be an inhibitor of adenosine deaminase in particular. See, *e.g.*, Sheid, *Res. Commun. Chem. Pathol. Pharmacol.* 47:149-152 (1985); Abstract provided in Exhibit D.

9. Thus, we conceived of the present invention based on the recognition that any antidepressant having an ability to modulate adenosine levels as one of its biological effects, could be used in methods for producing local analgesia and incorporated into compositions as claimed in the present application.

10. The experiments summarized in our previously submitted declaration using amitriptyline provide proof that an exemplary antidepressant could be used in methods for producing local analgesia and incorporated into compositions as claimed. Therefore, these experiments provide demonstrative evidence that we had the requisite means to produce the claimed compositions for local administration comprising any antidepressant and a vehicle suitable for topical administration.

11. Additional experiments were diligently performed following these preliminary studies over a period of less than 7 months, which are reflected in the specification as filed in the original priority application, USSN 09/081,709, filed on May 19, 1998 (now issued as U.S. Patent No. 6,211,171). Exhibit E.

12. We each individually further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

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Date

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Jana Sawynok

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Date

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Mike Esser

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Date

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Allison Reid